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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

| EXAMINER | |
|---|---|
| HUMPHREY, LOUISE WANG ZHIYING | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/555,534 | ENSOLI, BARBARA | |
| | Examiner | Art Unit | |
| | LOUISE HUMPHREY | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *192-196 and 198* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/8/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 62,63,65,66,68,69,89-103,105-112,114,116,117,119,121-123,142-165,167,168,179,181-196 and 198-207.

Continuation of Disposition of Claims: Claims rejected are 62,63,65,66,68,69,89-103,105-112,114,116,117,119,121-123,142-165,167,168,179,181-191 and 199-207.

## DETAILED ACTION

This Office Action is in response to the amendment filed 08 January 2009. Claims 1-61, 64, 67, 70-88, 104, 113, 115, 118, 120, 124-141, 166, 169-178, 180 and 197 have been cancelled. New claims 199-207 are added. Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 142-165, 167, 168, 179, 181-196 and 198-207 are pending. Claims 192-196 and 198 are withdrawn.

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 142-165, 167, 168, 179, 181-191 and 199-207 are currently examined.

### *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on 08 May 2008 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A copy of signed and initialed 1449 form is hereby attached.

### *Affidavit or Declaration under 37 CFR 1.132*

The third declaration of Dr. Magnani under 37 CFR 1.132 filed on 08 January 2009 is insufficient to overcome the rejection of claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 142-153, 155-162, 164, 165, 167, 168, 179 and 181-186 based upon the references, Chang *et al.* (11 October 1997) in view of Sumner-Smith *et al.* (US 5,646,120, patented 8 July 1997) and as evidenced by Gu *et al.* (1994), as set

forth in the last Office action because it represents a departure from Examiner's rationale in combining the cited prior art.

Professor Magnani states that if the Tat protein is lyophilized after RP-HPLC, and suspended in an aqueous, pH-buffered, neutral solvent, the Tat protein regains its native conformation and biological activity; however, if the biologically active Tat protein and remaining TFA after RP-HPLC elution, lyophilization, and resuspension is exchanged with another acid in an aqueous solvent, the three dimensional conformation of the Tat protein to be damaged by the acid. It is unclear how Applicant interprets the combination of cited prior art to mean the latter procedure that damages Tat conformation but not the former procedure that regains the native conformation and biological activity of the Tat protein. Examiner clarifies that the rejection never states that the combination of prior art suggests the sequential steps in such an order as exchanging cleavage acid with a pharmaceutically acceptable acid "after RP-HPLC elution, lyophilization, and resuspension" as contended by Applicant. Applicant has distorted Examiner's reasoning and rationale to mean in a different way that would obviously not be pursued by one skilled in the art. The obviousness of exchanging the cleavage acid right after the elution of the RP-HPLC or any protein column chromatography, but before lyophilization and resuspension, flows naturally from the teaching in the cited prior art.

Furthermore, the third Magnani declaration discusses the technical detail of the phase separation method of Gu *et al*. and states that the Tat protein would not exist in

the aqueous phase and thus would not be operable for extraction of Tat protein. However, the phase separation method is irrelevant to the rejection at issue because it is an extraneous fact not cited in the fact.

An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a prima facie case of obviousness. *In re Burckel*, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). See MPEP §716.02(e) [R-2]. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 127, 128, 166 and 180 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicants' cancellation of the claims.

The new matter rejection of claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 142-165, 167, 168, 179, and 181-191 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is withdrawn. Applicant's arguments filed 08 January 2009 have been fully considered but

they are not persuasive. However, upon further consideration and review of the prior art, this rejection is withdrawn.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 127, 128, 166 and 180 under 35 U.S.C. §103(a) as being obvious over Chang *et al.* (11 October 1997) in view of Sumner-Smith *et al.* (US 5,646,120, patented 8 July 1997) and as evidenced by Gu *et al.* (1994) is **withdrawn** in response to Applicants' amendment cancelling the claims.

The rejection of 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 142-153, 155-162, 164, 165, 167, 168, 179 and 181-186 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al.* (11 October 1997) in view of Sumner-Smith *et al.* (US 5,646,120, patented 8 July 1997) and as evidenced by Gu *et al.* (1994) is **maintained** for reasons of record and extended to new claims 199-203, 205 and 206.

The instant claims are directed to a composition comprising an isolated Tat protein in combination with a pharmaceutically acceptable carrier or excipients, wherein

said isolated Tat protein is biologically active and acceptable for administration to a human.

Chang *et al*. teach a composition comprising fully biologically active HIV Tat proteins, which are isolated by successive rounds of high-pressure liquid chromatography (HPLC) and ion-exchange chromatography (IEC), stored by lyophilization at -70°C and resuspended in degassed buffer, PBS containing 0.1% BSA and 0.1 mM DTT to prevent oxidation and loss of biological activity before use (page 1424, left column, Tat protein and anti-Tat antibody).

Chang *et al*. does not expressly teach combining the Tat protein with a pharmaceutically acceptable carrier or excipient to form a composition. However, the lyophilization process disclosed by Chang *et al*. necessarily removes the acetonitrile, as evidenced by Gu *et al*., who discloses that ACN is removed by evaporation or freeze-drying (Abstract).

Gu *et al*. further discloses removing organic solvents such as acetonitrile and trifluoroacetic acid (TFA) at the end of the protein preparation. During phase separation of acetonitrile-water mixture in protein purification, wherein the an effluent fraction containing 65% (vol.) acetonitrile/35% water/0.1% TFA is stored in a freezer at -17°C for several hours or overnight, the bottom phase containing 65% water, which contains 99%+ of the total protein, and 35% acetonitrile remains unfrozen (page 258, right column, first two paragraphs) and this reduced volume of solvent can be easily lyophilized, which removes acetonitrile.

Sumner-Smith *et al*. discloses that a peptide purified by HPLC and IEC is typically then treated to exchange the cleavage acid (e.g. TFA) with a pharmaceutically acceptable acid, such as acetic acid, to provide a water soluble salt of the peptide (column 9, lines 47-62). For therapeutic use, proteins exhibiting pharmaceutical grade purity are combined with pharmaceutically acceptable carriers to generate compositions suitable for administration to patients (column 10, lines 19-34).

Chang *et al*. also discloses purification of HIV Tat protein by heparin affinity chromatography (page 1424, bottom of left column). Even though there is no suggestion to avoid the use of PMSF in Chang *et al*., applicant has admitted on the record, as evidence by the two Magnani declarations (page 2 of the supplemental declaration filed on 19 October 2007), that it is common knowledge and routine experimentation in the art as of 1 December 1997 that a combination of purification steps should decrease levels of endotoxin in the resulting protein preparation and to avoid the use of PMSF in the process by purifying a protein at a pH or a temperature, e.g. near 0°C, that inactivates proteases without harming the protein of interest.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HIV-1 Tat composition of Chang *et al*. so as to make a composition of active Tat protein with a pharmaceutically acceptable carrier or excipient with a reasonable expectation of success because the prior art suggests the procedure to exchange the TFA for therapeutic use, to lyophilize the protein for storage and removal of traces of organic solvents, and to combine with pharmaceutically acceptable carriers to generate compositions suitable for administration to patients.

The skilled artisan would have been motivated to do so to generate a Tat composition acceptable for administration to patients. There would have been a reasonable expectation of success since one skilled in the art has been routinely removing the acetonitrile by lyophilization, as evidenced by Gu *et al*. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Response to Arguments***

Applicant's arguments filed 08 January 2009 have been fully considered but they are not persuasive. Applicants repeated the arguments that were already presented in the response filed on 08 May 2008. However, the Examiner's reasoning is re-iterated as follows:

Applicant stated on page 20 of the remark filed 8 January 2009 that the specification teaches the desirability of administering a biologically active Tat protein to a human (see page 10, lines 4-8 and 12-14; and page 14, lines 16-20) and methods for obtaining a composition comprising biologically active Tat protein, including the methods of Chang *et al*. (see page 25, lines 5-8 and 11-14). Applicant asserts that methods for modifying the procedures disclosed in the specification so as to avoid acetonitrile, TFA, and PMSF are well known in the art, as evidenced by the Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 filed May 1, 2007 ("First Magnani Declaration") and the Supplemental Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 filed October 22, 2007 ("Supplemental Magnani Declaration"), Applicant

later discounts this statement in her argument against the prior art rejection by contending that the Third Ensoli Declaration shows the prejudice in the prior art and clear skepticism and disbelief by experts in the art that taught away from administration of biologically active Tat protein in humans due to the knowledge that biologically active Tat protein had many activities that were believed to result in harmful health effects (see ¶17), as previously presented in the Amendment Under 37 C.F.R. § 1.114 filed May 8, 2008 (see pages 20-23).

Applicant's argument pertaining to Sumner-Smith's disclosure of transactivation-deficient compounds is not germane to the rejection at issue because such a teaching is not relied upon in the rationale of the rejection. Applicant's argument that Sumner-Smith's disclosure of exchanging the cleavage acid (e.g. TFA) with a pharmaceutically acceptable acid would be expected to destroy the biological activity of the Tat protein lacks evidentiary basis, even though Applicant submits the Third Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 ("Third Magnani Declaration"). Professor Magnani states that if the Tat protein is lyophilized after RP-HPLC, and suspended in an aqueous, pH-buffered, neutral solvent, the Tat protein regains its native conformation and biological activity; however, if the biologically active Tat protein and remaining TFA after RP-HPLC elution, lyophilization, and resuspension is exchanged with another acid in an aqueous solvent, the three dimensional conformation of the Tat protein to be damaged by the acid. It is unclear how Applicant interprets the combination of cited prior art to mean the latter procedure that damages Tat conformation but not the

former procedure that regains the native conformation and biological activity of the Tat protein. Examiner clarifies that the rejection never states that the combination of prior art suggests the sequential steps in such an order as exchanging cleavage acid with a pharmaceutically acceptable acid "after RP-HPLC elution, lyophilization, and resuspension" as contended by Applicant. Applicant has distorted Examiner's reasoning and rationale to mean in a different way that would obviously not be pursued by one skilled in the art. The obviousness of exchanging the cleavage acid *right after* the elution of the RP-HPLC or any protein column chromatography, *but before* lyophilization and resuspension, flows naturally from the teaching in the cited prior art. It would be immediately apparent and well within knowledge of one skilled in the art to perform an acid exchange reaction right after the column elution for immediate removal of toxic organic solvents, but before lyophilization and resuspension, because lyophilization is an art-recognized routine experimentation for the purpose of long term storage and preservation of protein activity while resuspension is a step commonly known in the art for reconstituting a lyophilized protein prior to use or administration. Therefore, the third Magnani declaration filed 08 January 2009 represents a departure from Examiner's rationale for combining the cited prior art as evidence of obviousness.

Most importantly, Applicant has not provided any evidence distinguishing the claimed invention from the prior art disclosure of isolated HIV Tat protein in Change *et al.*, in combination with the procedure for making a composition by combining with a pharmaceutically acceptable carrier or excipient as suggested by Gu *et al.* and Sumner-

Smith *et al.* Applicant has only presented arguments asserting that the prior art Tat protein does not possess the property or characteristic of being biologically active and being suitable for administration to human. However, the "wherein" clause reciting "biologically active" and "pharmaceutically acceptable for administration to a human" is not given patentable weight because the intended use does not materially limit the claimed composition to a particular chemical structure that distinguishes over the prior art Tat protein composition. Even Applicant herself admits that this claim limitation is an attribute or characteristic of the claimed composition, and is not a use limitation (see page 16 of the Remark filed on 24 October 2007). Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure.

Applicant further argues that the Gu *et al*. does not teach or suggest that lyophilization alone would remove the acetonitrile sufficient to produce a composition pharmaceutically acceptable for administration to a human. However, this argument mischaracterizes the rejection as if Gu *et al*. is the only reference relied upon. This argument does not outweigh the obviousness evidence as a whole, which contains an additional reference, Sumner-Smith *et al*., teaching the additional approach of treating purified peptide with pharmaceutically acceptable acid to exchange the cleavage acid. The third Magnani declaration filed on 08 January 2009 analyzing the technical detail of the phase separation method of Gu *et al*. is irrelevant to the rejection at issue. The phase separation method is an extraneous fact that is not related to the claimed

invention. The Gu *et al*. is cited as evidence to support the fact that lyophilization removes all the liquid in a protein solution, which would remove organic solvents.

Finally, Applicant's argument regarding the lack of reason for modifying an isolated Tat protein to be suitable for administration to a human is solely based on the inventor, Dr. Ensoli's opinion that Tat protein had many activities that were believed to result in harmful health effects. However, an opinion expressing doubt about the harmful health effects of the protein is not evidence showing nonobviousness. The cited prior art explicitly suggests combining a purified protein with pharmaceutically acceptable carriers to generate compositions suitable for administration to patients. Examiner clearly articulated the reasoning with some rational underpinning to support the legal conclusion of obviousness. Therefore, a *prima facie* case of obviousness is properly established.

The rejection of 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 114, 119, 142-153, 155-162, 164, 165, 167, 168, 179, 181-186 and 189 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al*. (11 October 1997) in view of Sumner-Smith *et al*. (US 5,646,120, patented 8 July 1997) and Heiman *et al*. (1998), as evidenced by Gu *et al*. (1994) is **maintained** for reasons of record.

The instant invention is further limited to an isolated HIV Tat protein fused to HIV Rev, Nef or Gag, or an immunogenic fragment thereof.

The relevance of Chang *et al*., Sumner-Smith *et al.* and Gu *et al*. is set forth above. These references do not disclose fusing HIV Tat to other HIV protein.

The review article by Heiman *et al.* describes numerous combinations of HIV proteins known in the art. They specifically disclose Gag at pages 3-5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine or fuse the HIV Tat protein of Chang *et al.* with the HIV Gag antigen of Heiman *et al.* so as to link the Gag immune response with the Tat protein immune response with the expectation of at least an additive effect. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Response to Arguments***

Applicants repeated the arguments against Chang *et al.*, Sumner-Smith *et al.*, and Gu *et al.* as set forth above, which have been fully considered but they are not persuasive for the same reasons as indicated above.

The rejection of 62, 63, 65, 66, 68, 69, 89-97, 101-103, 105-111, 116, 117, 121, 122, 142-165, 167, 168, 179, 181-187, 190 and 191 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al.* (11 October 1997) in view of Sumner-Smith *et al.* (US 5,646,120, patented 8 July 1997) and Vogel *et al.* (1995), as evidenced by Gu *et al.* (1994) is **maintained** for reasons of record and extended to new claims 204 and 207.

The instant invention is further limited to a HIV-1 Tat protein fused to a cytokine, specifically, IL-12, and added an adjuvant such as alum.

The relevance of Chang et al., Sumner-Smith et al. and Gu et al. is set forth above. These references do not disclose fusing HIV Tat to a cytokine like IL-12 or adding an adjuvant such as alum.

Vogel et al. discloses that IL-2 modulates the immune System through the T cell pathway. See entire reference. Vogel et al. further discloses that alum is a well known and studied adjuvant. As the authors note in the introductory paragraph on page I, alum is the only adjuvant used in human vaccine licensed in the United States.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add this cytokine to the composition of Chang et al. so as to link the favorable immune response with the Tat protein with the expectation of favorably modulating the immune system. It would have been further obvious to one of ordinary skill in the art at the time the invention was made to add a well known adjuvant, alum, to the composition of Chang et al. with the expectation of enhancing the immune reaction to Tat. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

### ***Response to Arguments***

Applicants repeated the arguments against Chang *et al.*, Sumner-Smith *et al.*, and Gu *et al.* as set forth above, which have been fully considered but they are not persuasive for the same reasons as indicated above.

The rejection of 62, 63, 65, 66, 68, 69, 89-96, 98, 99, 101-103, 105-109, 111, 142-153, 155-162, 164, 165, 167, 168, 179 and 181-186 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al.* (11 October 1997) in view of Sumner-Smith *et al.* (US 5,646,120, patented 8 July 1997) and Castignolles *et al.* (1996), as evidenced by Gu *et al.* (1994) is **maintained** for reasons of record.

The instant invention is further limited to a HIV-1 Tat protein bound to a nanoparticle.

The relevance of Chang et al., Sumner-Smith et al. and Gu et al. is set forth above. These references do not disclose binding HIV-1 Tat protein to a particle.

Castignolles et al. suggests that nanoparticles have immunostimulating properties. See the abstract and the discussion section.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the nanoparticles of Castignolles et al. with the Tat protein of Chang et al. with the expectation of enhancing the immune response to the protein. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

### ***Response to Arguments***

Applicants repeated the arguments against Chang *et al.*, Sumner-Smith *et al.*, and Gu *et al.* as set forth above, which have been fully considered but they are not persuasive for the same reasons as indicated above.

The rejection of 62, 63, 65, 66, 68, 69, 89-96, 98, 100-103, 105-109, 111, 142-153, 155-162, 164, 165, 167, 168, and 179-186 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al.* (11 October 1997) in view of Sumner-Smith *et al.* (US 5,646,120, patented 8 July 1997) and Ramshaw *et al.* (1977), as evidenced by Gu *et al.* (1994) is **maintained** for reasons of record.

The instant invention is further limited to a HIV-1 Tat protein bound to an autologous erythrocyte.

The relevance of Chang et al., Sumner-Smith et al. and Gu et al. is set forth above. These references do not disclose a HIV-1 Tat protein bound to an autologous erythrocyte.

Ramshaw et al. discloses that autologous erythrocytes (red blood cells) coupled to antigens can enhances an immune response of the antigen. See page 255.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to couple the HIV Tat protein of Chang et al. to autologous erythrocytes, as per the suggestion of Ramshaw et al., to enhance the immune response of the HIV Tat protein antigen. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

### ***Response to Arguments***

Applicants repeated the arguments against Chang *et al.*, Sumner-Smith *et al.*, and Gu *et al.* as set forth above, which have been fully considered but they are not persuasive for the same reasons as indicated above.

The rejection of 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 112, 142-153, 155-162, 164, 165, 167, 168, 179-186 and 188 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al.* (11 October 1997) in view of Sumner-Smith *et al.* (US 5,646,120, patented 8 July 1997) and Livingston *et al.* (August 1997), as evidenced by Gu *et al.* (1994) is **maintained** for reasons of record.

The instant invention is further limited to a HIV-1 Tat protein conjugated to a T-helper universal epitope of tetanus toxoid.

The relevance of Chang et al., Sumner-Smith et al. and Gu et al. is set forth above. These references do not disclose conjugating the HIV-1 Tat protein to a T-helper universal epitope of tetanus toxoid.

Livingston et al. suggests that conjugating the T helper epitope of tetanus toxoid to hepatitis B virus surface antigen (HBsAg) enhances the immunogenicity of the HBsAg. See the entire reference. Note that the reference teaches, on the first page, second column, that the T helper epitope of tetanus toxoid is a universal HTL epitope which greatly potentiates the CTL responses elicited by a vaccine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the T cell helper epitope of tetanus toxin of Livingston et al. to the HIV Tat protein of Chang et al. One would be motivated to do this in order to enhance the CTL response of the HIV Tat protein. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Response to Arguments***

Applicants repeated the arguments against Chang *et al.*, Sumner-Smith *et al.*, and Gu *et al.* as set forth above, which have been fully considered but they are not persuasive for the same reasons as indicated above.

The rejection of 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 123, 142-153, 155-162, 164, 165, 167, 168 and 179-186 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al.* (11 October 1997) in view of Sumner-Smith *et al.* (US 5,646,120, patented 8 July 1997) and Barry *et al.* (March 1997), as evidenced by Gu *et al.* (1994) is **maintained** for reasons of record.

The instant invention is further limited to a HIV-1 Tat protein combined with an inhibitor of viral replication.

The relevance of Chang et al., Sumner-Smith et al. and Gu et al. is set forth above. These references do not disclose adding an inhibitor of viral replication to the HIV-1 Tat protein.

Barry et al. discloses various viral inhibitor compounds known in the art. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add an antiviral inhibitor, as suggested by Barry et al., to the HIV Tat protein, as taught by Chen et al., in a combination therapy for an additive effect of viral inhibition. One skilled in the art would be motivated to do so for the inhibition of a

virus like HIV, which is known in the art to evolve into drug-resistant viral strains as a result of monotherapy. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

### *Response to Arguments*

Applicants repeated the arguments against Chang *et al*., Sumner-Smith *et al*., and Gu *et al*. as set forth above, which have been fully considered but they are not persuasive for the same reasons as indicated above.

### *Conclusion*

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

### *Correspondence*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/L. H./
Examiner, Art Unit 1648

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

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